REMARKS

Claims 1-8 and 12-28 are pending. Claims 9-11 stand withdrawn from consideration as being directed to nonelected subject matter, and claims 29 and 30 have been added. Claims 1-8 and 12-30 will therefore be pending upon entry of the proposed amendments.

Support for new claims 29 and 30 can be found throughout the Specification, e.g., at page 2, lines 16-19 and page 5, lines 8-12. No new matter is introduced by these amendments.

Rejection under 35 U.S.C. § 103

Claims 1-8 and 12-25 remain rejected as being unpatentable over Crumb et al., U.S. Patent 6,030,943 (Crumb) in view of Gyory et al., U.S. Patent 5,883,135 (Gyory).

Applicants respectfully traverse.

1. The present claims are directed to kits, pharmaceutical compositions, devices, and methods for the parenteral administration of didemnin compounds (e.g., aplidine, which is also known as dehydrodidemnin B). Claims 1-8 as currently amended are directed to kits that include "firstly a lyophilized didemnin preparation comprising water-soluble material and secondly, and separately contained, a reconstitution solution of mixed solvents." The kits provide a stable dosage form that can be reconstituted for administration by injection. Claims 12-25 are directed to reconstituted pharmaceutical compositions that include: a didemnin compound; a water soluble material; a surfactant; an alkanol; and water. Claim 29 is directed to an intravenous delivery device having disposed therein: a didemnin compound; a water soluble material; a surfactant; an alkanol; and water. Claim 30 is directed to a method for delivering a didemnin compound, which includes filling an intravenous delivery device with a didemnin compound; a water soluble material; a surfactant; an alkanol; and water.

2. The claimed kits, pharmaceutical compositions, devices, and methods address some of the problems associated with prior efforts to obtain stable, soluble pharmaceutical preparations that are suitable for the parenteral (e.g., intravenous) administration of didemnins. Stable didemnin pharmaceutical preparations can typically be achieved by the inclusion of a

bulking agent as part of the preparation. A preferred bulking agent for this purpose is mannitol, which is water soluble. The didemnins (e.g., aplidine), however, tend to have only rather limited water solubility. This difference in water solubility can be problematic for parenteral administration of didemnins, such as aplidine, because water-based vehicles are typically the liquid vehicles of choice for parenteral routes of administration. The inventors, in addressing the aforementioned problems, have discovered lyophilized didemnin preparations, which are both stable and permit solubilization of a didemnin (e.g., aplidine) and a water soluble adjuvant(s) (e.g., mannitol) in water based vehicles that are suitable for parenteral administration to a cancer patient.

3. The primary reference, Crumb, teaches aplidine compositions that can be used for intravenous administration. The secondary reference, Gyory, is only about transdermal administration and suggests to use a water-alcohol mix in transdermal devices for delivery of various drugs. The secondary reference is very largely (almost entirely) concerned with issues such as conductivity which are relevant specifically to transdermal delivery. There is no teaching or suggestion to select the aplidine composition disclosure of Crumb and combine it with the dermal delivery specific alcohol component of Gyory. This and other arguments are discussed in more detail below.

4. Crumb discloses that aplidine can be used as an L-type calcium channel enhancer (Crumb, col. 2, lines 33-34). Crumb teaches that aplidine can be administered "intravenously or by injection" using "liquids" that contain a single solvent, namely water (see Crumb at col. 6, lines 12-18). Mixed solvents as required by the present claims are never mentioned. In addition, while Crumb discloses lyophilized aplidine preparations, these preparations are expressly disclosed as being used in conjuction with reconstitution media that contain a single solvent--sterile water. Again, mixed solvents as required by the present claims are never mentioned.

5. Gyory is concerned exclusively with transdermal delivery of drugs (not a didemnin, didemnins are not mentioned in Gyory), stating: "this invention arose from a desire to improve on prior art technology in the field of transdermal electrotransport delivery" (Gyory at col. 3, lines 34-36). More specifically, Gyory discloses compositions for transdermal delivery that include a drug, a short chain alcohol, a long chain alcohol, and water. Gyory reports that the compositions reduce "electrical resistance of body surfaces, such as the skin, mucosa, and nails,"

thereby enhancing the "transdermal electrotransport drug flux" (Gyory at col. 3, lines 49-51 and col. 4, lines 60-64). Not only is Gyory unconcerned with parenteral administration, but Gyory also appears to be unconcerned with the drug solubilization issues facing the present inventors. In fact, Gyory specifically indicates that the drug being delivered is loaded into the transdermal delivery devices as "[a]n aqueous solution" (Gyory at col.8, line 27, emphasis added).

6. Mere fact that elements of a claimed invention are found in two (or more) prior art references is not sufficient to defeat patentability. To complete the *prima facie* case of obviousness, the Office must provide evidence that there was some motivation or suggestion in the prior art references to make the combination of elements claimed by Applicants. See, e.g., *In re Kotzab* 55 USPQ2d 1313, 1316 (Fed. Cir. 2000) (emphasis added):

> Most if not all inventions arise from a combination of old elements. *See In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998). Thus, every element of a claimed invention may often be found in the prior art. *See id.* **However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention**. *See id.* **Rather to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant**. *See In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998); *See In re Gordon*, 733 F.2d 900, 902, 221 USPQ2d 1125, 1127 (Fed. Cir. 1984).

See also, e.g., *In re Rouffet* 47 USPQ2d 1453, 1457-1458 (1998) (emphasis added):

> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. **In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the prior art references for combination in the manner claimed.**

The motivation or suggestion can be found in: (1) "the teachings of the prior art," (2) "the knowledge of persons of ordinary skill in the art," and (3) "the nature of the problem to be solved" (*In re Rouffet* 47 USPQ2d at 1458).

7. There is no showing of motivation to combine Crumb and Gyory in the manner claimed by Applicants in any of the three sources identified in *Rouffet*. This is discussed in more detail below.

First, as discussed in detail in the previous response, there is no motivation in Crumb and/or Gyory to make the combination of elements claimed by the Applicants. There is no teaching or suggestion in Crumb to use delivery or reconstitution media other than water-based media, much less mixed solvent delivery or reconstitution media that include alkanols and water. There is no teaching in Gyory that the water or alcohol or mixture of the two should or could be used to reconstitute a lyophilized preparation of any drug, let alone didemnin and, e.g., a bulking agent. Thus, there is no suggestion in Crumb and Gyory, either alone or taken together, to first select the alcohols disclosed in Gyory and then combine them with the aplidine compositions found in Crumb.

Second, the Office has argued that combining the elements disclosed in Crumb and Gyory in the manner claimed is "merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan" (Office Action, page 4). However, the Office cannot simply rely on the high level of skill as for a showing of a motivation to combine prior art references. Rather, the Office must "explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination" (*In re Rouffet* 47 USPQ2d at 1458). The Office's showing of motivation in the knowledge of persons of ordinary skill in the art does not meet legal standard set forth in *Rouffet*.

Lastly, and perhaps even more importantly, the Office provides no reasons that one of skill in the art, seeking to prepare stable, soluble pharmaceutical preparations that are suitable for the **parenteral** (e.g., intravenous) administration of didemnins, would combine the teachings of Crumb with the teachings of Gyory, the latter of which not only fails to mention didemnins (lyophilized or otherwise), but has nothing to do with parenteral administration. More

specifically, the Office provides no reasons that one of skill in the art, seeking to enhance the solubility of didemnins in water based vehicles that are suitable for parenteral administration, would combine the Crumb compositions with a component (i.e. the alcohols in Gyory) having the single, and completely unrelated, disclosed function of reducing "electrical resistance of body surfaces, such as the skin, mucosa, and nails" (Gyory at col. 3, lines 49-51). As mentioned elsewhere, not only is Gyory unconcerned with parenteral administration, but Gyory also appears to be unconcerned with the water solubility of the drugs being delivered. Gyory specifically mentions that his contemplated drugs for delivery could be handled in a seemingly routine manner as aqueous solutions (see Gyory at col.8, lines 26-27).

Thus, the problems addressed by Gyory (enhancement of electrotransport of therapeutic agents across body surfaces) is very different from, and completely unrelated to, the problems faced by the present inventors (e.g., to provide a stable dosage form that can be wholly reconstituted for administration by injection).

Further, Gyory's attempts to solve the problem of dermal permeability has nothing to do with what is disclosed and fairly suggested by Crumb. One reference, Crumb, is at best, about reconstitution of a lyophilized solution. The other, Gyory, is about dermal electrotransport. There is no teaching in Gyory to start with a lyophilized preparation and no teaching that the mixed solvent would be useful or work to reconstitute a lyophilized preparation, let alone a lyophilized preparation of didemnin. Gyory simply teaches that its solution, i.e., drug, water, and alcohol, is useful in a transdermal device for movement of the drug into the skin. So, Crumb teaches one solvent (water) for the purpose of rehydrating a lyophilized preparation. Gyory teaches a different solution (alcohol and water) for a different use, i.e., a liquid to contain a drug in a transdermal device. There is no mention of rehydrating a lyophilized preparation in Gyory.

In short, a the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention would not have been motivated to combine Gyory with Crumb in a manner that would render the claimed invention obvious.

There is no showing of any motivation to combine Crumb and Gyory in the manner claimed by Applicants in any of the three sources identified in *Rouffet*: (1) "the teachings of the prior art," (2) "the knowledge of persons of ordinary skill in the art," and (3) "the nature of the problem to be solved" (*In re Rouffet* 47 USPQ2d at 1458). Lacking such a showing, the Office's

prima facie case is incomplete. In view of the foregoing, Applicants respectfully request that the rejection be withdrawn.

Applicants submit that all claims are in condition for allowance.

Enclosed is a $450 check for the Two Month Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No.: 14620-012US1.

Respectfully submitted,

Date: June 26, 2006

Allen T. Kendall
Reg. No 50,650

For Louis Myers
Reg. No. 35,965

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

21257986.doc